This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Final Draft 6/30/93

# CENTER FOR DEVICES AND RADIOLOGICAL HEALTH'S PREMARKET APPROVAL APPLICATION (PMA) REFUSE TO FILE POLICY

## PURPOSE

The Office of Device Evaluation (ODE) receives up to 100 original Premarket Approval Applications (PMAs), and hundreds of major PMA supplements every year. Many of these applications are incomplete or grossly inadequate, fail to contain the components necessary to allow substantive review of the application and inappropriately consume scientific resources when they are assigned to Center scientists for evaluation. As a means to employ more effectively the Center's scientific resources, procedures will be implemented to ensure that PMAs, and PMA supplements with substantial new information relating to the safety and effectiveness of the device, meet a minimum threshold of acceptability; otherwise the Center will refuse to file the application. These procedures will benefit both FDA and application sponsors.

## DISCUSSION

The Center's goal in establishing a Refuse to File (RTF) Policy for PMA applications is to improve the use of our review resources by ensuring that they are focused on the review of reasonably complete and well-supported applications. Often, during initial scientific review, the Center has found that crucial information clearly necessary to make a decision to approve or not to approve the device has been omitted. When making a decision to file or not to file an application, the Center intends to distinguish between applications in which sufficient information is submitted to allow a decision on the approvability of the device (i.e. the application is complete on its face) and those applications where the information is substantially incomplete and no meaningful assessment can be made. A decision to refuse to file an application should be distinguished from a decision to find the device not approvable after a full review. By establishing a Refuse to File Policy with criteria that are clear, consistent, and available to sponsors, they will know what is expected of them for their PMA. Sponsors will be likely to comply with the established criteria to speed the time to substantive review and regulatory decision.

While we can refuse to file those PMAs that have not met a baseline threshold for completeness based on the regulatory requirements, this alone will not upgrade the scientific quality of incoming applications. Therefore, we must continue to promulgate product specific guidelines or guidance documents describing our scientific/technical expectations. In instances where we have established clear expectations in a guidance document, we can evaluate the quality of an application against the consideration the sponsor has given the scientific/technical issues addressed in the guidance.

The minimum threshold determination for filing the PMA application, i.e., whether the application merits a substantive evaluation by Center scientists, will be made in accordance with the ODE Blue Book memorandum (PMA Memorandum P90-2). This memorandum, addressing the filing review, indicates that such a threshold determination is in fact consistent with the intent of the law, regulations and the overall philosophy of the office. In addition, the Biometrics staff has initiated procedures that will identify "fatal flaws" in the application's statistics that would preclude a meaningful statistical assessment of the clinical data.

## RECOMMENDATIONS

As a result of the above considerations, the following recommendations are hereby made to establish and implement a Refusal to File Policy for PMAs:

1. Train reviewers to implement the Refuse to File Policy. The Program Operations Staff will conduct the initial training and provide ongoing support for the implementation of the RTF policy within the review Divisions.

2. Implement a checklist for use in the initial review of all PMAs. Examples of the proposed checklist for PMAs can be found attached to this document. Divisions may modify or supplement this general list based on available guidance documents appropriate to their specific product areas.

3. Guidelines or guidance documents should be promulgated wherever such needs are identified. Guidances should provide specific details about what is expected and acceptable for all components of the submissions. Each product specific guideline should include a checklist to be used by a) the applicant in preparing the submission and b) FDA reviewers during the initial evaluation

to consider filing the application. Checklists should be prepared for existing guidelines. These checklists and guidance documents should be made available to industry through the Division of Small Manufacturers' Assistance (DSMA). This will save time and provide consistency across submissions. Emphasis also should be placed on improved communication with industry.

IMPLEMENTATION

The Refuse to File Policy will be implemented by the review Divisions within the Center's Office of Device Evaluation utilizing the procedures provided in the document PMA Refuse To File Criteria. The timeframe for a decision to file or not to file a PMA will continue to be 45 days as described in the Blue Book Memo P90-2, PMA Filing Decisions. Implementation of the Refuse to File Policy will be monitored on a quarterly basis by the Office of the Director, ODE, to determine if criteria are being applied consistently across Divisions and in accord with the policy. Adjustments will be made in application of the policy as necessary.

EFFECTIVE DATE

The PMA Refuse to File Policy is effective immediately.

CONCURRENCE

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## PMA REFUSE TO FILE CRITERIA

As a means to more effectively utilize review resources and to improve the timeliness of the device evaluation process, the Center is establishing a Refuse to File Policy for Premarket Approval Applications (PMAs).

With PMAs, the filing stage is the logical point to make a threshold determination regarding the quality of the submission and whether the application merits a substantive evaluation by agency scientists. The ODE Blue Book memorandum governing the filing review indicates that such a threshold determination is in fact consistent with the intent of the law, regulations and overall philosophy of the office.

The purpose of the attached PMA Checklist for Filing Decision is to: provide uniform guidance as to when a PMA should be filed or not filed; ensure that regulatory obligations are met; ensure consistency of filing reviews among the Divisions; and to upgrade the quality of applications. It is intended that this checklist will be used to separate those PMAs which are sufficiently complete to allow an in-depth scientific review from those that are lacking important regulatory elements or are so grossly deficient in some element that, in effect, the element has not been provided. If the Center has provided product specific guidelines or guidance documents to industry, these documents are to be used in conjunction with the "PMA Checklist for Filing Decision". The reviewer should keep in mind that the purpose of the filing review is to ensure reviewability not approvability of the PMA.

There are three parts to the PMA Checklist for Filing Decision:

**"Part A"** identifies those elements that the PMA submission must contain to allow substantive review of the application. A PMA sponsor must provide the elements listed in "Part A", provide a justification for the omission for any missing element, or request a waiver to omit a section where there is provision for waiver of that part. The reviewer will determine if the sponsor has adequately addressed each element. A PMA deficient in any "Part A" element, whether due to being grossly inadequate or omitted without justification, should not be filed.

**"Part B"** identifies those elements required by the PMA regulation but which do not, individually, support a decision to refuse to file an application. Those deficiencies should be communicated to the sponsor in a separate section of the letter appropriate for the decision (file or not file).

**"Part C"** contains elements not required by the PMA regulations and also not intended for use to support a decision to refuse to file an application. The elements in "Part C" provide important information for Office of Device Evaluation management consideration. "Part C" is followed by decision and signature elements.

Sponsors are still expected to submit information as required by the Act, the implementing regulations, and as described in the PMA Manual. The PMA Checklist for Refusal to File an Application is an aid to the sponsor and the reviewer and is NOT a new PMA contents outline.

**To use this checklist** place a check mark in the "Yes" block (left hand column) when: the item is present and adequate; a justification for an omitted item has been provided; or a waiver has been requested. Place a check in the "No" block (right hand column) when the item is grossly inadequate or omitted without a valid justification.

ANY "NO" RESPONSE CHECKED IN "PART A" SHOULD RESULT IN A REFUSE TO FILE DECISION.

**A decision memo must** be included with this checklist which provides the rationale for the decision as well as a brief explanation for all "No" answers and any other minor questions included in the decision letter.

The Not Filed letter must be accompanied by a completed PMA Checklist for Filing Decision, the decision memo, the statistical checklist, and any product specific guidance or guideline.

# THE PMA CHECKLIST FOR FILING DECISION

Identification:

PMA Number: _____ Date Received: _____

Sponsor: _____

Device: _____

Division/Branch: _____

Decision:

Recommendation: File __ Not File __

Administrative Reviewer Signature: _____ Date: _____

Supervisory Signature: _____ Date: _____

# THE PMA CHECKLIST FOR FILING DECISION

**PART A** - DEFICIENCIES TO BE INCLUDED AS REASONS FOR NOT-FILING THE PMA

| Filing Review Elements | Yes<br>Present<br>Omission Justified | No<br>Inadequate<br>Omitted |
|---|---|---|
| I. **Organizational and Administrative Elements**<br>(21 CFR 814.20, Blue Book Memo #P-90-2) | | |
| A. Are key administrative items present?<br>(CFR 814.20(a), 814.20(b)(1) and 814.20(b)(2)) | ☐ | ☐ |
| B. Is PMA organization sufficient to permit substantive review? | ☐ | ☐ |
| C. Is device appropriate for review in class III? | ☐ | ☐ |
| D. The regulations do not allow the FDA to file a PMA if a 510(k) for the same device is pending. Has the applicant withdrawn any pending 510(k)? If no stop review!<br>(21 CFR 814.42(e)(3)) | ☐ | ☐ |
| E. If this device has been the subject of an NSE decision, does the PMA address the NSE issues (e.g., new material, energy source, etc.)? | ☐ | ☐ |
| F. Are you aware of the applicant being the subject of an integrity investigation? If yes, consult the ODE integrity officer. Has the ODE Integrity Officer given permission to proceed with the review?<br>(Blue Book Memo #I91-2, 21 CFR 814.42(e)(4) and Federal Register 90N-0332, September 10, 1991) | ☐ | ☐ |
| G. Is there is a prior history of sponsor with this device? For example, has a previously submitted PMA for this device been withdrawn? If yes, does the current PMA address any historical issues related to fraud, safety, or effectiveness? | ☐ | ☐ |
| II. **Do the data submitted in support of this PMA constitute valid scientific evidence?**<br>(21 CFR 860.7) | ☐ | ☐ |

| Filing Review Elements | Yes<br>Present<br>Omission Justified | No<br>Inadequate<br>Omitted |
|---|---|---|
| **III. Summary of Safety and Effectiveness Data**<br>(Blue Book Memo #P86-1) | | |
| A. Are indications for use provided? | ☐ | ☐ |
| B. Is an abbreviated device description provided? | ☐ | ☐ |
| C. Is a summary of the studies provided?<br>(21 CFR 814.20(b)(3)) | ☐ | ☐ |
| 1. Is a summary of the non-clinical laboratory studies and results provided? | ☐ | ☐ |
| 2. Is a summary of the clinical investigations and results provided? | ☐ | ☐ |
| D. Are conclusions drawn from the studies provided?<br>(21 CFR 814.20(b)(3)(vi)) | ☐ | ☐ |
| 1. Is a discussion demonstrating that PMA information provides reasonable assurance of the safety and effectiveness of the device for its intended use provided? | ☐ | ☐ |
| 2. Is a risk/benefit analysis provided? | ☐ | ☐ |
| **IV. Labeling**<br>(21 CFR 814.20(b)(10) and Blue Book Memo #P91-4) | | |
| A. Has appropriate draft labeling been submitted (e.g., Physician, Patient, Technical, etc.)? | ☐ | ☐ |
| **V. Device Characteristics and Manufacturing Sections**<br>(Note: **may be waived for filing purposes** and submitted later during the substantive review period; OCS reviews prior to GMP inspection for GMP issues; ODE reviews for safety and effectiveness issues)<br>(21 CFR 814.20(b)(4)(v) and Guidance for the Preparation of PMA Manufacturing Information) | | |

A. Is a description of device, pictorial representations, and materials specifications present?
(21 CFR 814.20(b)(4)(i)) ☐ ☐

B. Is a description of the principles of operation of the device (including components) and properties relevant to clinical function present?
(21 CFR 814.20(b)(4)(iii)) ☐ ☐

C. Has a description of the methods, facilities, and controls used in the manufacture, processing, packing, storage, and installation of the device been provided?
(21 CFR 814.20(b)(4)(v)) ☐ ☐

VI. **Nonclinical Laboratory Studies**
(21 CFR 814.20(b)(6)(i))

A. Microbiological ☐ ☐

B. Toxicological ☐ ☐

C. Immunological ☐ ☐

D. Biocompatibility ☐ ☐

E. Stress ☐ ☐

F. Wear ☐ ☐

G. Shelf life ☐ ☐

H. Analytical (for IVDs) ☐ ☐

I. Have other pertinent device/material-specific laboratory animal tests have been provided? ☐ ☐

J. Has the applicant provided documentation to establish conformance with applicable standard and/or FDA guidance/guidelines?
(21 CFR 814.20(b)(5)) ☐ ☐

## VII. Clinical Investigations
(21 CFR 814.20(b)(6)(ii))

A. Is there an adequate description of clinical utility? (Blue Book Memo #91.1) ☐ ☐

B. If the PMA is supported by a sole investigator, has a justification been provided? (21 CFR 814.20(b)(7)) ☐ ☐

C. Is reference to applicable IDEs given? IDE#_____ ☐ ☐

D. Are clinical protocols described and included? ☐ ☐

1. Are numbers of investigators and subjects per investigator specified? ☐ ☐
2. Is a description of subject inclusion and exclusion criteria provided? ☐ ☐
3. Has a description of the study period been provided? ☐ ☐
4. Have clinically significant endpoints been selected? ☐ ☐

E. Was safety and effectiveness data provided? (21 CFR 814.20(b)(6)(ii)) ☐ ☐

1. Was the clinical study completed as specified in the protocol (e.g., number of patients completing the study, follow-up period, follow-up evaluations, single device design, etc.)? ☐ ☐
2. Is a description of study population demographics provided? ☐ ☐
3. Is a description of adverse events, e.g. adverse reactions, complaints, discontinuations, failures, replacements, etc. given? ☐ ☐
4. Are statistical analyses of the clinical investigations provided? ☐ ☐
5. Have all appropriate FDA requirements applicable to the device and/or clinical study been met? ☐ ☐

6. Are foreign clinical data included? ☐ ☐

   If yes, are data justified and acceptable? (21 CFR 814.15(b) and 814.15(d)) ☐ ☐

7. Has all information reasonably known to the sponsor and relevant to the safety and effectiveness evaluation been provided? (21 CFR 814.20(b)(8)(ii)) ☐ ☐

F. Has documentation and conformance with applicable standard and/or FDA guidance/guidelines been provided? (21 CFR 814.20(b)(5)) ☐ ☐

G. Does the OST Statistician recommend filing? ☐ ☐

H. Have report forms for patients who died or were discontinued been provided, i.e., to resolve potential bias? (Goal: 100% accountability) ☐ ☐

VIII. **Is there any other reason not addressed above which should be identified as a reason for not filing the PMA? If so, briefly explain.** ☐ ☐

_____

_____

_____

_____

PART B - DEFICIENCIES TO BE INCLUDED IN THE "MINOR" SECTION OF THE NOT-FILING OR FILING BOILERPLATE LETTER

| Additional Filing Review Elements | Yes | No |
|---|---|---|
| **IX. Additional Administrative and Organizational Elements** | | |
| A. If there are color additive considerations has an attempt been made to document them? (21 CFR 814.20(f)) | ☐ | ☐ |
| B. Is a bibliography provided? (21 CFR 814.20(b)(8)(i)) | ☐ | ☐ |
| Have copies of key articles been provided and are English translations included, if appropriate? | ☐ | ☐ |
| C. Do we need a device sample? | ☐ | ☐ |
| If yes, has it been provided? (21 CFR 814.20(b)(9)) | ☐ | ☐ |
| **X. Additional Regulatory Requirements** | | |
| A. Have alternative practices been included and described? (21 CFR 814.20(b)(3)(iii)) | ☐ | ☐ |
| B. Is the description of prior marketing history provided? (814.20(b)(3)(iv)) | ☐ | ☐ |
| C. Was the clinical study conducted in compliance with Part 56 (IRB), Part 50 (informed consent), or Parts 812 or 813 (IDE)? (21 CFR 814.20(b)(6)(ii)(A) and 21 CFR 814.20(b)(6)(ii)(B)) | ☐ | ☐ |
| D. Has the data presented in the PMA taken into account the staff concerns addressed in the IDE? | ☐ | ☐ |

E. If there are environmental considerations has an attempt been made to document them or a claim of categorical exclusion has been requested? (21 CFR 814.20(b)(11)) ☐ ☐

**PART C - ADDITIONAL CONSIDERATIONS**

| | Yes | No |
|---|---|---|
| **XI. Additional Considerations** | | |
| A. Can the GMP inspection be initiated within an appropriate timeframe? If the manufacturing section has been waived or the manufacturing site(s) are not currently ready for inspection, check the NO box. | ☐ | ☐ |

B. Are there any special administrative issues? If so, explain. _____

_____

_____

C. Are there any precedent setting substantive issues? If so, explain. _____

_____

_____

D. Procode assigned? Identify _____

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